

**STATUS OF CLAIMS:**

Claims 1-4, 6, 7, 9-11, 13-15 and 17-30 were pending in the application.  
Claims 21-23 are allowed.  
Claims 1, 11, 15, 18, 19, 24-26, 28, and 30 are amended herein.  
Claims 9, 13, 14, 27, and 29 are canceled herein.  
Claims 1-4, 6-7, 10-11, 15, 17-20, 24-26, 28 and 30 are presented for reconsideration.

**REMARKS**

Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks.

The allowance of claims 21-23 is noted with appreciation.

Claims 1, 11, 15, 18, 19, 24-26, 28, and 30 have been amended to more particularly point out and distinctly claim the subject matter of Applicants' invention. Support for the amendments can be found, for example, in original claims 1-30. No new matter has been added.

Applicants thank the Examiner for the courtesy of conducting a telephonic interview on Tuesday, June 24, 2003. In the interview, Applicants discussed the claims that were submitted to the USPTO via facsimile transmission on June 19, 2003. The Examiner indicated that claims 1-4, 6-7, 10-11, 15, and 17-20 were in a condition for allowance as submitted. However, Applicants were unable to reach an agreement regarding the outstanding rejection of claims 24-29 under 35 U.S.C. § 112, first paragraph, based on the route of administration of the codon-optimized HPV16 polynucleotides of the present invention (*see* Office Action, page 4). It was further agreed that since the aforementioned rejection was made for the first time in the Office Action mailed March 27, 2003, and was not necessitated by Applicants' amendment or based on an Information Disclosure Statement submitted by Applicants; finality of the Office Action will be removed.

Consistent with 37 C.F.R. § 1.121, a version of the amended claims with markings to show changes resulting from the above amendments is presented at the end of this response.

***Rejections under 35 U.S.C. § 112, Paragraph 1***

Claims 1-4, 6, 9, 10, 13, 14, 17, 19, 20, and 24-30 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that has not been adequately described in the

specification to convey to one skilled in the art that the inventors had possession of the invention. These claims are also rejected based on the enablement requirement of 35 U.S.C. § 112, allegedly because "a disclosure cannot teach one to make or use something that has not been described" (see Office Action at page 4).

Applicants submit that this rejection is rendered moot by the above-mentioned telephonic interview, in which the Examiner indicated that claims 1-4, 6, 9, 10, 13, 14, 17, 19, and 20, as submitted via facsimile on June 19, 2003 and as presented herein, are allowable.

Claims 24-29 are also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the claimed invention. Specifically, the Office Action states that the specification "does not reasonably provide enablement for inducing a protective immune response to *any* serotype HPV infection in a subject using a polynucleotide encoding a codon-optimized HPV16 protein by *any* route of administration." (Emphasis in original.) Applicants respectfully traverse.

This two-part rejection may be summarized as follows: (1) the specification does not provide enablement for inducing an immune response to any serotype HPV infection and (2) the specification does not provide enablement for inducing an immune response to HPV infection in a subject using a polynucleotide encoding a codon-optimized HPV16 protein by any route of administration.

In response to part (1) of this rejection, Applicants have amended the preamble of claims 24-26 and 28 to indicate that the claims are drawn to a method of inducing an immune response to *HPV16*. Applicants assert that claims 24-26 and 28, as amended, are in condition for allowance and respectfully request that the rejection be removed and the claims allowed. Applicants further note that the rejection of claims 27 and 29 is rendered moot by their cancellation herein.

With respect to part (2) of the rejection, Applicants assert that the claims are commensurate in scope with the disclosure and that, therefore, it would, not require undue experimentation to make and use the claimed methods. In support of this position, it is noted that the initial burden of establishing a basis for questioning the enablement provided for the claimed invention rests with the Examiner. See MPEP § 2164.04. In fact, teachings within the specification "must be taken as in compliance with the enabling requirement of the first paragraph of 112 unless there is a reason to doubt the objective truth of the statements contained therein." See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1967).

The claims at issue are drawn to a method of inducing an immune response to HPV16 by administering to a subject a polynucleotide encoding a codon-optimized HPV protein. Routes of administration of said polynucleotide taught by Applicants disclosure include, but are not limited to, subcutaneous, intradermal, intraperitoneal, intravenous, and intramuscular (*see* page 11, line 29 – page 12, line 2). In other words, the claims encompass any mode of administration provided that *any* immune response to HPV16 results.

The Office Action doubts the objective truth of Applicants disclosure, allegedly because “the specification fails to teach whether the claimed method could induce an immune response in a subject by any route of administration...” *See* Office Action at page 5. The Office Action further alleges that “in view of the limited guidance, the lack of predicatability of the art and the breadth of the claims, one skill (sic) in the art could not practice the invention without undue experimentation.” *Id.* The thrust of the Examiner’s argument is as follows: different modes of delivery of DNA vaccines produce quantitatively and qualitatively different immune responses. In support of this assertion, the Office Action cites two references in support of its position that Applicants specification is not enabled. The first, McCluskie et al. (*Mol. Med.* 5: 287-300 (1999)), is cited for teaching that the strength and nature of immune responses to HBsAg in mice and non-human primates differs depending on the mode of administration. Nakano et al. (*J. Virol.* 71: 7101-09 (1997)) is cited for a similar teaching using plasmids encoding different domains of HCV E2.

In response thereto, Applicants submit that the cited references fail to prove that Applicants claims are not enabled because the contested claims are drawn to a method of inducing *any* immune response to HPV16, whether or not the mode of administration chosen by one of skill in the art results in the strongest or most desirable immune response. Which method would provide the *best* immune response is irrelevant to the question of enablement, and, therefore, not a deficiency of Applicants’ specification. Both Applicants disclosure and the scientific art at the time of filing teach that DNA-based vaccines can be administered by various methods and result in an immune response. *See*, for example, the disclosure by McCluskie et al. (p. 288, column 2), who state that “DNA vaccines have been delivered to a wide variety of tissues by both injected and noninjected DNA delivery methods...” and provide >25 examples of DNA vaccines delivered by numerous methods (*see* p. 288, column 2, bridging p. 289, column 1).

In response to the Examiner’s statement that “[t]he specification fails to teach whether the claimed method could induce an immune response in a subject by any route of administration,” Applicants note that there is no requirement in § 112 or any other patent law that the specification provide “a specific example of everything *within the scope* of a broad

claim.” *In re Anderson*, 176 USPQ 331 at 333 (CCPA 1973), emphasis in original. See also *In re Angstadt and Griffin*, wherein the Court opined that

The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with “thousands” of examples.... More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed.

190 USPQ 214 at 218 (CCPA 1976).

Applicants submit that the claims are commensurate in scope with the disclosure, which exemplifies particular embodiments within the scope of the claims and also teaches how one of skill in the art can obtain other embodiments within the scope of the claims. Applicants specification discloses novel codon-optimized polynucleotides encoding HPV16 proteins and shows that said polynucleotides are immunogenic. Additionally, Applicants provide a working example showing that BALB/c mice immunized with the DNA V1Jns:16E2 developed CD4<sup>+</sup> immune responses to HPV when a novel HPV16E2-encoding polynucleotide of the present invention was administered via intramuscular injection (see EXAMPLE 8). These mice were significantly protected from tumor development compared to the control group. Applicants disclosure further teaches that any other delivery method may be used to introduce the novel polynucleotides to the subject. There is no reason to believe that delivery of codon-optimized HPV16 polynucleotides to a subject by other modes of delivery would be non-immunogenic.

Thus, it is Applicants position that it would not require undue experimentation to practice the claimed methods. As such, Applicants assert that claims 24-26 and 28 are in condition for allowance and respectfully request that the rejection of these claims be removed and the claims allowed.

#### **Office Action Finality**

MPEP § 706.07(a), mandates that second actions on the merits can properly be made final, *except* where the Examiner introduces a new ground of rejection that is neither necessitated by Applicants’ amendment nor based on information submitted in an information disclosure statement (IDS). The outstanding rejection of claims 24-29 under 35 U.S.C. § 112, first paragraph, based on the route of administration of the codon-optimized HPV16 polynucleotides of the present invention (*see* Office Action, page 4) was presented for the first time in the current Office Action, mailed March 27, 2003. Because this rejection was not

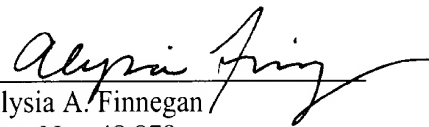
necessitated by Applicants' amendment or based on an IDS submitted by Applicants, finality of the present Office Action was improper. Applicants discussed this issue with the Examiner during a telephonic interview on Tuesday, June 24, 2003, who agreed to remove finality of the Office Action. Therefore, the current response is being treated as an amendment under 37 C.F.R. § 1.111.

### Summary

It is believed that the claims are in a condition for allowance and a favorable action on the merits is earnestly solicited.

If the Examiner believes that a telephone conference would be of value, she is requested to call the undersigned attorney at the number listed below.

Respectfully submitted,

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**Version Showing Markings of Pending Claims**

1. (Twice Amended) A synthetic polynucleotide comprising a sequence encoding a codon-optimized human papillomavirus serotype 16 (HPV16) protein[, or mutated form thereof which has reduced protein function for viral replication and cellular transformation as compared to wild-type protein, but which maintains immunogenicity,] wherein said polynucleotide sequence comprises codons that are optimized for expression in a human host.
2. A polynucleotide according to Claim 1 wherein the protein is selected from the group consisting of: L1, L2, E1, E2, E4, E5, E6 and E7.
3. A polynucleotide according to Claim 2 wherein the protein is selected from the group consisting of: L1, E1, E2, and E7.
4. A polynucleotide according to Claim 2 which is DNA.
6. A polynucleotide according to Claim 4 wherein the protein is an HPV16 L1 protein.
7. A polynucleotide according to Claim 6 which comprises the polynucleotide of FIGURE 1 (SEQ.ID.NO: 1).
- [9. A polynucleotide according to Claim 4 wherein the protein is a mutated form of E1.]
10. A polynucleotide according to Claim [9] 4 which is an HPV16 E1 protein.
11. (Amended) A synthetic polynucleotide [according to Claim 10] which comprises a sequence of nucleotides as set forth in [the polynucleotide of] FIGURE 2 (SEQ.ID.NO:2).
- [13. A polynucleotide according to Claim 4 wherein the protein is a mutated E2 protein.]

[14. A polynucleotide according to Claim 13 which is an HPV16 E2 mutated protein.]

15. (Amended) A synthetic polynucleotide [according to Claim 14] which comprises a sequence of nucleotides as set forth in [the polynucleotide of] FIGURE 3 (SEQ. ID.NO: 3).

17. A polynucleotide according to Claim 4 wherein the protein is an HPV16E7 protein.

18. (Amended) A synthetic polynucleotide [according to Claim 17] which comprises a sequence of nucleotides as set forth in [the polynucleotide of] FIGURE 4 (SEQ. ID.NO:4).

19. (Twice Amended) An adenoviral vaccine vector comprising an adenoviral genome with a deletion in the E1 region, and an insert in the E1 region, wherein the insert comprises an expression cassette comprising:

- a) a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins [or mutant forms thereof], wherein said polynucleotide is codon-optimized for expression in a human host cell; and
- b) a promoter operably linked to the polynucleotide.

20. A vector according to Claim 19 wherein the adenoviral genome also contains a deleted E3 region.

21. (Previously Amended) A shuttle plasmid vector comprising a plasmid portion and an adenoviral portion, the adenoviral portion comprising: an adenoviral genome with a deletion in the E1 region, and an insert in the E1 region, wherein the insert comprises an expression cassette comprising:

- a) a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins, wherein said polynucleotide is codon-optimized for expression in a human host cell; and
- b) a promoter operably linked to the polynucleotide.

22. A vaccine plasmid comprising a plasmid portion and an expression cassette portion, the expression cassette portion comprising:

- a) a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins, wherein said polynucleotide is codon-optimized for expression in a human host cell; and
- b) a promoter operably linked to the polynucleotide.

23. A plasmid according to Claim 22 wherein the plasmid portion is V1Jns.

24. (Twice Amended) A method for inducing immune responses to HPV16 in a human subject [vertebrate] which comprises administering to [a vertebrate] the subject between 1 ng and 100 mg of the composition of Claim 1 [to the vertebrate].

25. (Twice Amended) A method for inducing immune responses to HPV16 in a human subject [vertebrate] which comprises administering to [a vertebrate] the subject between  $10^{11}$ - $10^{12}$  particles of an adenoviral vector carrying the composition of Claim 1 [to the vertebrate].

26. (Twice Amended) A method for inducing an immune response against human papillomavirus type 16 (HPV16) in a human subject [vertebrate], comprising

a) administering to [a vertebrate] the subject a first vector comprising a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins, wherein said polynucleotide is codon-optimized for expression in a human host cell;

b) allowing a predetermined amount of time to pass; and

c) administering to said [vertebrate] subject a second vector comprising adenoviral vaccine vector comprising an adenoviral genome with a deletion in the E1 region, and an insert in the E1 region, wherein the insert comprises an expression cassette comprises

i) a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins [or mutant forms thereof], wherein said polynucleotide is codon-optimized for expression in a human host cell; and

ii) a promoter operably linked to the polynucleotide.

[27. A method according to Claim 26 wherein the vertebrate is human.]



28. (Twice Amended) A method for inducing immune responses to HPV16 in a human subject [vertebrate] comprising

a) administering to [a vertebrate] the subject a plasmid vaccine, wherein the plasmid vaccine comprises a plasmid portion and an expression cassette portion, the expression cassette portion comprising:

i) a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins, wherein said polynucleotide is codon-optimized for expression in a human host cell; and

ii) a promoter operably linked to the polynucleotide;

b) allowing a predetermined amount of time to pass; and

c) administering to said [vertebrate] subject an adenoviral vaccine vector comprising an adenoviral genome with a deletion in the E1 region, and an insert in the E1 region, wherein the insert comprises an expression cassette comprising:

i) a polynucleotide encoding a codon-optimized HPV16 protein selected from the group consisting of L1, E1, E2, and E7 proteins [or mutant forms thereof], wherein said polynucleotide is codon-optimized for expression in a human host cell; and

ii) a promoter operably linked to the polynucleotide.

[29. A method according to Claim 28 wherein the vertebrate is human.]

30. (Twice Amended) A method of making a codon-optimized HPV16 protein comprising expressing in a human host cell a synthetic polynucleotide encoding a human papillomavirus serotype 16 (HPV16) protein, [or mutated form thereof which has reduced protein function for viral replication and cellular transformation as compared to wild-type protein, but which maintains immunogenicity,] wherein said polynucleotide sequence comprises codons optimized for expression in a human host.